CLAIMS

1. A formulation comprising a complex between an estrogen and a cyclodextrin, wherein the formulation is a granulate preparation, said granulation preparation having a relative humidity of at most 60%, as determined at a temperature between 20°C and 40°C.

2. The formulation according to claim 1, wherein the granulate preparation has a relative humidity of at most 55%, as determined at a temperature between 20°C and 40°C.

3. The formulation according to claim 1, wherein the granulate preparation has a relative humidity of at most 45%, as determined at a temperature between 20°C and 40°C.

4. The formulation according to claim 1, wherein the granulate preparation has a relative humidity of at most 40%, as determined at a temperature between 20°C and 40°C.

5. The formulation according to claim 1, wherein the estrogen is selected from the group consisting of ethinyl estradiol (EE), estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, and estrone sulfate or mixtures thereof.

6. The formulation according to claim 5, wherein the estrogen is selected from the group consisting of ethinyl estradiol (EE), estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, and estrone sulfate or mixtures thereof.

7. The formulation according to claim 6, wherein the estrogen is ethinyl estradiol.

8. The formulation according to claim 1, wherein the cyclodextrin is selected from the group consisting of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin and derivatives thereof.

9. The formulation according to claim 8, wherein the cyclodextrin is β-cyclodextrin or derivatives thereof.

10. The formulation according to claim 1 comprising at most 2% w/w of polyvinylpyrrolidone of polyvinylpyrrolidone.

11. The formulation according to claim 1 comprising at most 1% w/w of polyvinylpyrrolidone of polyvinylpyrrolidone.

12. The formulation according to claim 1 comprising at most 0.5% w/w of polyvinylpyrrolidone of polyvinylpyrrolidone.

13. The formulation according to claim 1 comprising at most 0.2% w/w of polyvinylpyrrolidone of polyvinylpyrrolidone.

14. The formulation according to claim 1 further comprising one or more therapeutically active agent(s).

15. The formulation according to claim 14, wherein the one or more therapeutically active agent(s) is a progestogen.

16. The formulation according to claim 15, wherein the progestogen is selected from the group consisting of drospirenone, levonorgestrel, norgestrel, gestodene, dienogest, cyproterone acetate, norethisterone, norethisterone acetate, desorgestrel, 3-keto-desorgestrel.

17. The formulation according to claim 16, wherein the progestogen is drospirenone.

18. The formulation according to claim 17, wherein the drospirenone is micronized.

19. The formulation according to claim 16, wherein the estrogen is ethinyl estradiol and the one or more therapeutically active compound is drospirenone.

20. The formulation according to claim 1, wherein the complex is micronized.

21. The formulation according to claim 1 further comprising an antioxidant.

22. The formulation according to claim 1, wherein the estrogen is in an amount relative to the cyclodextrin such that a molar ratio between the estrogen and the cyclodextrin is from about 2:1 to 1:10.

23. The formulation of claim 22, wherein the molar ratio is from about 1:1 to 1:5.

24. The formulation of claim 22, wherein the molar ratio is from about 1:1 to 1:3.

25. A composition comprising:

i) a complex between an estrogen and a cyclodextrin; and

ii) one or more excipients,

the composition having a stability such that said estrogen is in amount of at least 85% w/w in relation to the initial content of said estrogen after storage for 12 months at 40°C and 75% relative humidity (RH).

26. The composition according to claim 25, wherein the said complex between an estrogen and a cyclodextrin. is a granulate preparation having a relative humidity of at most 60%, as determined at a temperature between 20°C and 40°C.

27. The composition according to claim 25, wherein the estrogen is in an amount correspondent to a therapeutically equivalent amount of ethinyl estradiol of from about 0.002 % w/w to 2 % w/w.

28. The composition according to claim 25, wherein the estrogen is in an amount from about 0.002 % w/w to 2% w/w.

29. The composition according to claim 25, wherein the estrogen is in an amount from about 0.004% w/w to 0.2% w/w.

30. The composition according to claim 25, wherein the estrogen is ethinyl estradiol and the cyclodextrin is β-cyclodextrin, the ethinyl estradiol is in an amount relative to the ethinyl-estradiol-β-cyclodextrin complex of from about 5 % w/w to 20 % w/w.

31. The composition according to claim 25, wherein the estrogen is ethinyl estradiol and the cyclodextrin is β-cyclodextrin, the ethinyl estradiol is in an amount relative to the ethinyl-estradiol-β-cyclodextrin complex of from about 8% w/w to 15% w/w.

32. The composition according to claim 25 further comprising drospirenone in an amount from about 0.4 % to 20% w/w.

33. The composition according to claim 25 further comprising drospirenone in an amount from about 0.8% w/w to 10% w/w.

34. The composition according to claim 25 further comprising drospirenone in an amount from about 1.5 % w/w to 5% w/w.

35. A method for inhibiting ovulation in a female comprising administering a combination of i) a complex between an estrogen and a cyclodextrin and ii) drospirenone, wherein the combination is comprised in a composition as defined in claim 32.

36. A method for hormone replacement therapy in a female comprising administering a combination of i) a complex between an estrogen and a cyclodextrin and ii) drospirenone, wherein the combination is comprised in a composition as defined in claim 32.

37. A method for improving the stability of an estrogen in a pharmaceutical composition that comprises an estrogen and one or more excipients in a granulate preparation, the method comprises the steps of:

i) forming a complex between said estrogen and a cyclodextrin; and

ii) mixing under granulation conditions the said complex with the one or more excipients such that the relative humidity of the final granulate does not exceed 60%, as determined at a temperature between 20°C and 40°C.

38. The method according to claim 37, wherein the one or more excipients comprises polyvinylpyrrolidone in an amount of at most 2% w/w.

39. The method according to claim 37, wherein the one or more excipients comprises polyvinylpyrrolidone in an amount of at most 1% w/w

40. The method according to claim 37, wherein the one or more excipients comprises polyvinylpyrrolidone in an amount of at most 0.5% w/w.

41. The method according to claim 37, wherein the one or more excipients comprises polyvinylpyrrolidone in an amount of at most 0.2% w/w.

42. A process for manufacturing a granulate preparation comprising a complex between an estrogen and a cyclodextrin, wherein the processing of the granulate preparation comprises the steps of:

i) loading the complex, optionally further one or more therapeutically active agent(s) and one or more excipients into a granulator;

ii) applying a liquid onto the loaded complex and the one or more excipients under granulation conditions so as to obtain granules having a relative humidity not exceeding 60%, as determined at a temperature between 20°C and 40°C.

43. The process according to claim 42, wherein the complex and the optionally further one or more therapeutically active agent(s) are provided as individual agent(s) without being pre-mixed with excipients.

44. The process according to claim 42, wherein the relative humidity of the granulate preparation does not exceed 55%, as determined at a temperature between 20°C and 40°C.

45. The process according to claim 42, wherein the relative humidity of the granulate preparation does not exceed 45%, as determined at a temperature between 20°C and 40°C.

46. The process according to claim 42, wherein the relative humidity of the granulate preparation does not exceed 40%, as determined at a temperature between 20°C and 40°C.

Substitute Sheet (Rule 26)